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14. ABSTRACT Background: An outbreak of trauma-related invasive fungal infections (IFI) occurred in US service members injured in Afghanistan. Empiric treatment included voriconazole (VORI) and amphotericin (AMB) and aggressive surgical debridement. Antifungal susceptibilities (AS) and relation to outcoID Week, San Diego, CA, Oct 5 2017mes are yet to be described. Methods: Between 2009-2013, military trauma patients with initial unique and serial (>3 days after initial isolation) molds isolated from wounds and admitted to Brooke Army Medical Center as part of the Trauma Infectious Disease Outcomes Study were assessed. The AS to AMB, VORI, posaconazole (POSA), isavuconazole (ISA), itraconazole, and caspofungin were determined by broth microdilution with CLSI breakpoint interpretations for Aspergillus spp. and mucormycetes (MM). Results: Included are 18 patients with 28 initial mold isolates with 72% of IFI diagnosed via histopathology. All patients were male with a median of 8 operations. There was a median of 11 days post-injury to mold culture. Initial isolates were 5 Aspergillus spp., 3 MM, 3 Fusarium spp., and co					
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ANTIFUNGAL RESISTANCE PATTERNS IN MOLDS ISOLATED FROM WOUNDS OF COMBAT-RELATED TRAUMA PATIENTS

Poster

Nicholas Keaton, MD,¹ Katrin Mende, PhD,^{1,2,3} Miriam L. Beckius, MPH,¹ Aaron Farmer, DO,⁷ Julie Rizzo, MD,^{4,5} Anuradha Ganesan, MD,^{2,3,6} Clinton K. Murray, MD,¹ David R. Tribble, DrPH, MD,² Dana M Blyth, MD¹AFFILIATIONS: ¹San Antonio Military Medical Center, Fort Sam Houston, TX; ²Infectious Disease Clinical Research Program, Department of Preventive Medicine and Biostatistics, Uniformed Services University of the Health Sciences, Bethesda, MD; ³Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc., Bethesda, MD; ⁴Department of Surgery, Uniformed Services University of the Health Sciences, Bethesda, MD; ⁵United States Army Institute of Surgical Research, Fort Sam Houston, TX; ⁶Walter Reed National Military Medical Center, Bethesda, MD; ⁷Womack Army Medical Center, NC

Abstract

Background: An outbreak of trauma-related invasive fungal infections (IFI) occurred in US service members injured in Afghanistan. Empiric treatment included voriconazole (VORI) and amphotericin (AMB) and aggressive surgical debridement. Antifungal susceptibilities (AS) and relation to outcomes are yet to be described.

Methods: Between 2009-2013, military trauma patients with initial unique and serial (>3 days after initial isolation) molds isolated from wounds and admitted to Brooke Army Medical Center as part of the Trauma Infectious Disease Outcomes Study were assessed. The AS to AMB, VORI, posaconazole (POSA), isavuconazole (ISA), itraconazole, and caspofungin were determined by broth microdilution with CLSI breakpoint interpretations for *Aspergillus* spp. and mucormycetes (MM).

Results: Included are 18 patients with 28 initial mold isolates with 72% of IFI diagnosed via histopathology. All patients were male with a median of 8 operations. There was a median of 11 days post-injury to mold culture. Initial isolates were 5 *Aspergillus* spp., 3 MM, 3 *Fusarium* spp., and combinations of 3 *Aspergillus* & MM, 2 *Aspergillus* & *Fusarium*, 1 *Aspergillus* & *Bipolaris*, 1 MM & *Fusarium*. *A. flavus* (AFL) and *A. fumigatus* (AFU) were all susceptible to AMB and POSA and 25% of AFL were intermediate to VORI. Four *A. terreus* (AT) isolates had MICs to AMB of 0.25, 1, 2, and 4, and were susceptible to VORI. ISA MIC50 and 90 were 1 and 2 for *Aspergillus* spp. *Fusarium* spp. MICs were >16 for VORI, POSA, and ISA, with AMB MIC50/90 of 2 and 3. Among MM isolates, 86% were susceptible to AMB and 29% to POSA, and ISA MIC50 and MIC90 were 8 and >16. Five patients had serial isolates. One with serial AFL and AFU received no antifungal therapy, one with AT was treated with VORI, AMB, and POSA, and one with AFL was treated with AMB with no new resistance. The patient with serial MM was treated with AMB and VORI and remained resistant to POSA, but susceptible to AMB. Serial *A. elegans* acquired new POSA and AMB resistance and ISA MIC increased from 4 to 16 after AMB and VORI exposure.

Conclusion: Antifungal exposure to AMB and VORI was not associated with new resistance within *Aspergillus* spp., but 50% of MM exposed to this combination developed POSA and AMB resistance. Despite resistance of *Fusarium*, it was not isolated on subsequent debridements.

Background

- Operation Enduring Force and Operation Iraqi Force were notable for an outbreak of trauma-related invasive fungal infections (IFI)
- IFI are associated with a high mortality in trauma patients
- IFI is independently associated with increased mortality in burn patients, particularly with TBSA 30-60%, with fungal wound infection being associated with the same mortality as augmenting the total body surface area of burn by 33%
- Current empiric antifungal therapy is broad-spectrum, primarily with voriconazole (VORI) and amphotericin (AMB)
- To reexamine treatment option with newer azoles, such as posaconazole (POSA) and isavuconazole (ISA), susceptibility studies on molds isolated from wounds of US service members treated at San Antonio Military Medical Center (SAMMC) were examined

Methods

- Susceptibility testing to AMB, VORI, POSA, ISA, itraconazole (ITRA), and caspofungin was performed using the Clinical and Laboratory Standards Institute (CLSI) M38-A2 broth microdilutions defined protocols for *Aspergillus* spp. and mucormycetes (MM)
- AMB, VORI, POSA, ISA, and ITRA were tested in ranges of 0.0313 µg/ml to 16 µg/ml and caspofungin at 0.015 µg/ml to 8.0 µg/ml
- Minimal Effective Concentration (MEC) was reported for caspofungin and MIC data was evaluated for all other antifungals
- Resistance patterns were utilized to build an antibiogram applying MIC50 and MIC90 utilizing CLSI recommended cutoffs as available
- Serial isolates from patients were also evaluated for changing antifungal resistance patterns
- Working CLSI breakpoints were used for *Aspergillus* spp. (AMB, VORI, POSA, and ITRA) and Mucormycetes (AMB, POSA): susceptible (MIC ≤ 1 µg/mL), intermediate (MIC 2 µg/mL), and resistant (MIC ≥ 4 µg/mL)

Results

- 18 male patients were analyzed with a total of 28 initial mold isolates with a median of 8 (ranging from 3-40) operations during their treatment course

Initial Mold Isolate Susceptibilities

Organism (# of isolates)	AMB MIC 50/90	VORI MIC 50/90	POSA MIC 50/90	ISA MIC 50/90	ITRA MIC 50/90
<i>Aspergillus</i> spp. (14)	0.25 / 2	0.5 / 2	<0.0313 / 0.125	1 / 2	0.125 / 0.25
<i>A. Fumigatus</i> (2)	0.125 / 0.25	0.25 / 0.5	<0.0313 / 0.125	1 / 1	0.125 / 0.25
<i>A. Flavus</i> (5)	0.25 / 1	1 / 2	<0.0313 / 0.0625	1 / 2	0.0625 / 0.125
<i>A. Terreus</i> (4)	1 / 4	0.5 / 1	<0.0313 / 0.0625	1 / 4	0.125 / 0.125
<i>A. flavus</i> complex (3)	0.25 / 0.5	1 / 2	<0.0313 / 0.125	2 / 2	0.25 / 0.25
<i>Fusarium</i> (6)	2 / 4	>16 / >16	>16 / >16	>16 / >16	>16 / >16
<i>Mucor</i> (4)	0.25 / 0.25	>16 / >16	2 / 4	8 / 16	>16 / >16

Results (cont.)

- Initial isolates included 5 *Aspergillus* spp., 3 Mucormycetes, 3 *Fusarium*, and combinations of 3 *Aspergillus* & Mucormycetes, 2 *Aspergillus* & *Fusarium*, 1 *Aspergillus* & *Bipolaris*, 1 Mucormycetes & *Fusarium*
- We tested 5 separate serial isolates to include 1 *Aspergillus terreus*, 2 *Aspergillus flavus*, 1 *Aspergillus fumigatus* complex, 1 *Actinomyces elegans*, and 1 *Mucor*

Selected Serial Mold Isolate Susceptibilities

Organism	AMB	VORI	POSA	ISA	ITRA
<i>Actinomyces elegans</i>					
3/29/12	0.5	4	1	0.5	16
3/31/12	1	4	1	0.5	16
4/2/12	0.125	16	>16	2	>16
4/4/12	2	16	2	1	>16
<i>Mucor</i>					
5/10/13	0.25	16	>16	2	>16
5/10/13	0.25	16	>16	2	>16
7/17/13	0.125	8	>16	2	>16
<i>A. flavus / fumigatus complex</i>					
7/20/12	0.5	0.125	<0.0313	0.25	<0.0313
7/20/12	0.25	1	<0.0313	1	0.125
7/20/12	0.25	1	<0.0313	2	0.0625
7/20/12	0.125	0.5	<0.0313	1	0.25
7/24/12	0.5	0.125	<0.0313	0.125	<0.0313
7/27/12	0.25	0.125	<0.0313	0.25	<0.0313
7/27/12	0.125	1	0.0625	1	0.25
7/31/12	0.25	1	<0.0313	1	0.25

Results (cont.)

- No significant resistance was noted in the 4 *Aspergillus* isolates examined
- Fusarium* spp. MIC were >16 for voriconazole, posaconazole, and isavuconazole
- Antifungal exposure to voriconazole and amphotericin was not associated with new resistance within the *Aspergillus* spp.
- Half of the Mucormycetes exposed to voriconazole and amphotericin developed posaconazole and amphotericin resistance

Conclusions

- Despite significant resistance, *Fusarium* was not isolated on subsequent debridements when treated with amphotericin and voriconazole
- Prior studies have shown *Fusarium* to not be a particularly virulent infection in cutaneous infections
- While amphotericin has significant toxicities, given inherent voriconazole resistance and elevated posaconazole and isavuconazole MICs noted in these Mucormycetes (and their frequent recovery), amphotericin appears to remain an important agent as part of empiric therapy
- Posaconazole demonstrated overall comparable susceptibility to voriconazole providing evidence for the possibility of utilizing posaconazole as part of an empiric treatment regimen
- Overall due to low sample size both in initial isolates and serial isolates further studies are required prior to deviating from AMB and VORI for initial empiric treatment of invasive fungal infections

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Correspondence

Nicholas Keaton, MD; Nicholas G. Keaton.mil@mail.mil